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Synthesis of the C1−C11 Western Fragment of Madeirolide A

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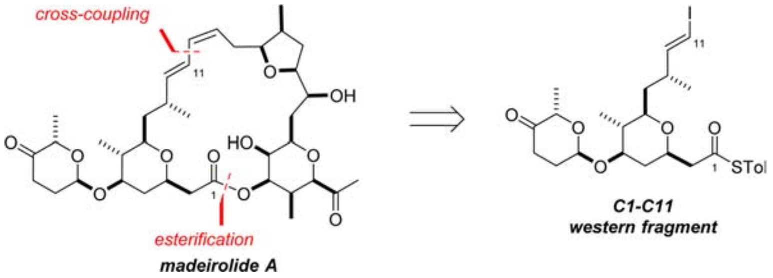
ABSTRACT



The stereocontrolled synthesis of a fully elaborated C1−11 subunit of madeirolide A is described, utilizing an asymmetric boron aldol reaction and a *cis*-selective hetero-Michael cyclization to form the tetrahydropyran ring, followed by efficient formation of the required C5 α-glycoside.

Marine sponges produce an extraordinary array of novel bioactive secondary metabolites and represent an important source of lead compounds for the development of new chemotherapeutic agents.[1] Lithistid sponges have proven particularly fertile in this respect,[2] serving as the source of potent antitumor polyketides such as dictyostatin,[2b] discodermolide,[2c] and more recently, leiodermatolide.[2d]

A notable addition to this impressive collection of marine natural products is the madeirolide family of macrolides (Scheme 1), which were recently disclosed by Wright and Winder at Harbor Branch.[3] Their structures were determined by detailed NMR spectroscopic analysis,[3] and their stereochemical assignment was further validated using Goodman's DP4 computational NMR method.[4] Madeirolide A (**1**) and B (**2**) were shown to be potent inhibitors of the fungal pathogen *Candida albicans* (fungicidal MIC = 12.5 (**1**)/25 (**2**) μg/mL). However, the scarcity of isolates from the sponge source (*Leiodermatium* sp.) has thus far hampered detailed evaluation of their antiproliferative properties. Given the established biological profile of the aforementioned polyketides of lithistid origin, and the nanomolar antitumor activity exhibited by their close structural relatives, mandelalides A and B,[5] this remains an intriguing unknown.

As part of our continued interest in the development of new therapeutic agents from marine natural products,[6] we identified the madeirolides as attractive synthetic targets because of their structural intricacy and tantalizing

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[1] (a) Blunt, J. W.; Copp, B. R.; Keyzers, R. A.; Munro, M. H. G.; Prinsep, M. R. *Nat. Prod. Rep.* **2012**, *29*, 144. (b) Dalby, S. M.; Paterson, I. *Curr. Opin. Drug Discovery Dev.* **2010**, *13*, 777. (c) Nicolaou, K. C.; Chen, J. S.; Dalby, S. M. *Bioorg. Med. Chem.* **2009**, *17*, 2290. (d) Paterson, I.; Anderson, E. A. *Science* **2005**, *310*, 451. (e) Driggers, E. M.; Hale, S. P.; Lee, J.; Terrett, N. K. *Nat. Rev. Drug Discov.* **2008**, *7*, 608. (f) Yeung, K.-S.; Paterson, I. *Angew. Chem., Int. Ed.* **2002**, *41*, 4632.

[2] (a) Winder, P. L.; Pomponi, S. A.; Wright, A. E. *Mar. Drugs* **2011**, *9*, 2643. (b) Isbrucker, R. A.; Cummins, J.; Pomponi, S. A.; Longley, R. E.; Wright, A. E. *Biochem. Pharmacol.* **2003**, *66*, 75. (c) ter Haar, E.; Kowalski, R. J.; Hamel, E.; Lin, C. M.; Longley, R. E.; Gunasekera, S. P.; Rosenkranz, H. S.; Day, B. W. *Biochemistry* **1996**, *35*, 243. (d) Paterson, I.; Dalby, S. M.; Roberts, J. C.; Naylor, G. J.; Guzmán, E. A.; Isbrucker, R.; Pitts, T. P.; Linley, P.; Divlianska, D.; Reed, J. K.; Wright, A. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 3219.

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[4] Smith, S. G.; Goodman, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 12946. See the Supporting Information for details of these DP4 calculations for madeirolide A. For a recent application see ref 2d.

[5] Sikorska, J.; Hau, A., M.; Anklin, C.; Parker-Nance, S.; Davies-Coleman, M., T.; Ishmael, J., E.; McPhail, K., L. *J. Org. Chem.* **2012**, *77*, 6066. The A rings of the madeirolides and mandelalides have the same absolute configuration, whereas the B rings are enantiomeric. The absolute configurations of the madeirolides and mandelalides were assigned by comparison to the cinerulose moiety of aclacinomycin A and degradation studies, respectively.

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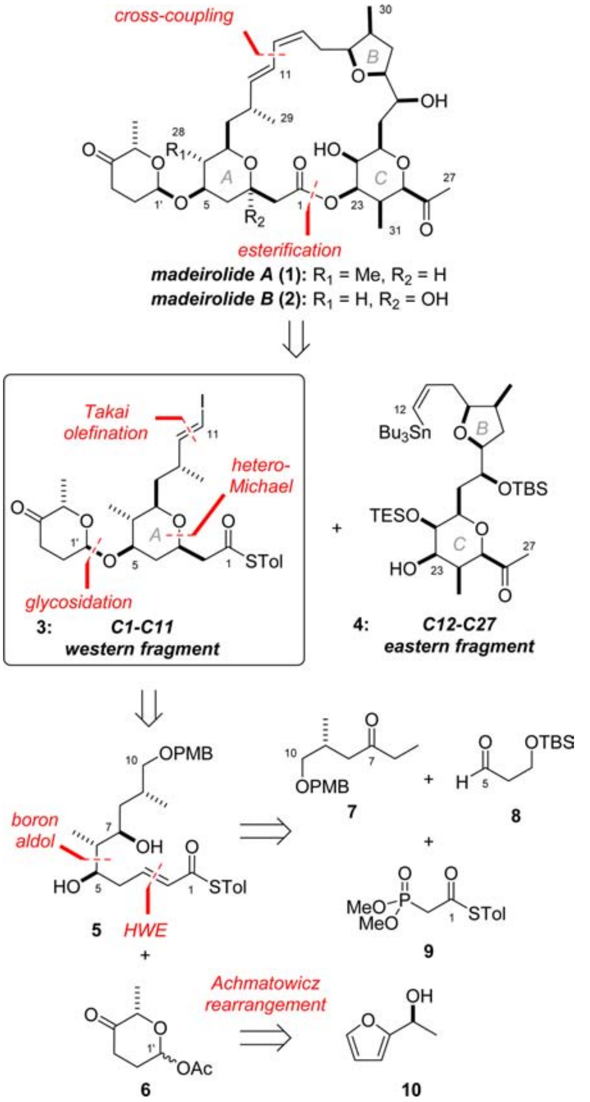
bioactivity, which may both be more fully explored through total synthesis. Herein, we report the first details of this work, leading to the preparation of a fully elaborated C1−C11 fragment of madeirolide A.

Scheme 1. Retrosynthetic Analysis of Madeirolide A



From a synthetic perspective, madeirolide A presents a considerable array of structural complexity. Some 16 stereocenters are embedded within a 24-membered macrolactone core featuring three distinct cyclic domains (A−C): the glycosylated A-ring and all-*cis*, pentasubstituted C-ring tetrahydropyrans, and the B-ring tetrahydrofuran. For maximal convergency and relative stereochemical flexibility, our approach sought to construct madeirolide A from preassembled, suitably functionalized A−C ring subunits, exploiting the intervening C10−C13 diene and C1 lactone linkages as ideal points for fragment union (Scheme 1). This reveals C1−C11 vinyl iodide **3** and C12−C27 vinyl stannane **4** as the targeted macrolide precursors, which might be coupled through a combination of Stille and esterification reactions. The C1−C11 vinyl iodide **3** would arise through hetero-Michael cyclization of thioester **5** to establish the 2,6-*cis*-tetrahydropyran,[7] followed by Takai olefination and glycosidation with cinerulose derivative **6**, itself formed through Achmatowicz rearrangement of (*S*)-2-furyl ethanol (**10**). Recognition of the C5−C6 *syn*-relationship indicated that the C5−C9 stereotetrad within thioester **5** might arise from ethyl ketone **7** and aldehyde **8** utilizing our boron aldol method,[8,9] followed by subsequent 1,3-*anti* reduction to establish the remaining C7 stereocenter.

As shown in Scheme 2, preparation of ethyl ketone **7** commenced from (*S*)-ester **11**,[10] which would serve as the source of the isolated C9 methyl-bearing stereocenter. Accordingly, reduction of **11** followed by mesylation and iodination of the resulting alcohol provided iodide **12**[11] (78%, three steps), which underwent smooth displacement with the lithium anion of dithiane **13**.[12] The masked ketone could then be revealed upon treatment of the dithiane adduct with aqueous iodine to give **7**.[13]

Coupling of ethyl ketone **7** and aldehyde **8**[14] with controlled installation of the C6 and C7 stereocenters was then carried out by way of a chiral ligand-mediated ((−)-Ipc$_2$BOTf, *i*-Pr$_2$NEt) boron aldol reaction, which provided the desired *syn* adduct **14** in excellent yield (93%) and as essentially a single diastereomer.[15]

With β-hydroxy ketone **14** in hand, the newly formed C5 alcohol stereochemistry could be faithfully (>95:5 dr) relayed to C7 through 1,3-*anti* reduction under Evans−Tishchenko conditions.[16] Methanolysis of the ensuing propionate ester and acetonide protection afforded the requisite C5−C9 stereotetrad as part of **15** (86%, three steps).[17] Removal of the TBS ether and oxidation with Dess-Martin periodinane then provided the C3−C10 aldehyde **16**, in readiness for HWE homologation to install an appropriate hetero-Michael acceptor for cyclization to form the 2,6-*cis*-substituted A-ring tetrahydropyran.

Initially, this took the form of enoate **18** (Scheme 3), prepared by Ba(OH)$_2$-mediated HWE olefination with

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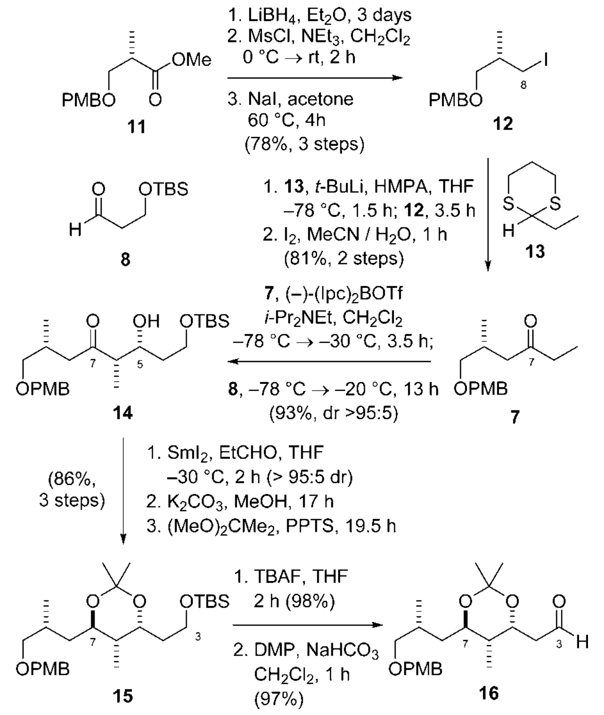
(17) (a) The C5/C7 *anti*-relationship was confirmed through ^{13}C NMR analysis of acetonide **15**, according to the method of Rychnovsky and Evans; see the Supporting Information for details. (b) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945. (c) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511. (d) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099.

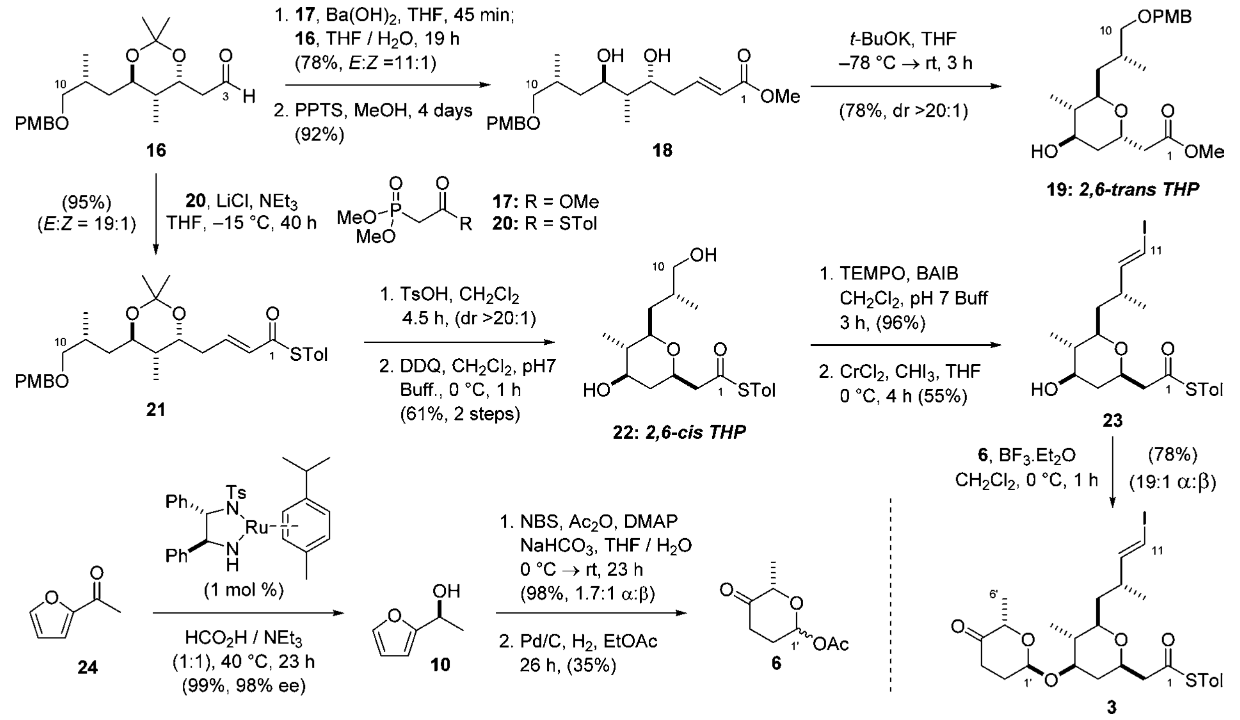
Scheme 2. Preparation of C3−C16 Aldehyde **16**



phosphonate **17** (78%, 11:1 (*E*):(*Z*)),[18] followed by acetonide deprotection (PPTS, MeOH, 92%). Subjection of **18** to a range of basic conditions[19] effected smooth cyclization but unexpectedly provided almost exclusively the 2,6-*trans*-tetrahydropyran **19**. All attempts to generate the desired 2,6-*cis* isomer (elevated reaction temperature/extended reaction time) proved unsuccessful. The failure to access the presumed thermodynamic 2,6-*cis* tetrahydropyran might be ascribed to intramolecular hydrogen-bonding with the C5 hydroxyl group favoring the formation of the 2,6-*trans* product through a boatlike transition state.[20] Accordingly, we explored the alternative thioester substrate **5**, which might allow for the desired mode of cyclization to occur under *acidic* conditions, as prescribed by Fuwa.[7] Condensation of aldehyde **16** with thioester phosphonate **20** under Masamune-Roush conditions[21] at −15 °C provided **21** in excellent yield and selectivity (95%, 19:1 (*E*)/(*Z*)). Gratifyingly, subjection of the corresponding diol arising from acetonide removal to Fuwa's conditions (CSA, DCE, 70 °C) effected selective (72%, >20:1 2,6-*cis*:*trans*) formation of the targeted 2,6-*cis* tetrahydropyran. After surveying a range of acidic conditions, acetonide removal and cyclization were optimally carried out as a one-pot operation through prolonged (6 h) exposure of **21** to TsOH·H$_2$O (0.5 equiv) in CH$_2$Cl$_2$ at ambient temperature. While this also resulted in partial PMB deprotection, the crude cyclized material could then be treated with DDQ to deliver the A-ring diol **22** in an efficient manner through this two-step sequence.

Diol differentiation of **22** could then be effected through selective primary oxidation.[22] The ensuing C10 aldehyde could then be homologated to vinyl iodide **23** through Takai olefination,[23] thus completing the synthesis of the C1−C11 madeirolide A aglycone fragment.

Scheme 3. Completion of the Western Fragment **3**



An appropriate cinerulose glycosyl donor, acetate **6**, was straightforwardly accessed in three steps from 2-acetylfuran (**24**). Noyori reduction of **24** provided enantioenriched alcohol **10** (99%, 98% ee),[24] which was then subjected to Achmatowicz rearrangement with in situ acetylation of the ensuing lactol to give acetate **6** as a mixture of anomers (ca. 1.7:1 α:β).[25] Hydrogenation then provided cinerulose donor **6** (35%).[26]

With both glycosyl donor **6** and acceptor **23** in hand, their union would complete the fully functionalized C1–C11 western hemisphere of madeirolide A. In the event, it was found that prolonged (18.5 h) exposure of a mixture of **6** and **23** to $BF_3 \cdot Et_2O$ (0.5 equiv) resulted in the smooth formation of the desired α-glycoside **3** in excellent yield and selectivity (78%, 19:1 α:β).

Detailed NMR comparisons of the madeirolide A C1–C11 glycoside **3** with the corresponding natural product data were carried out (Figure 1).[27] While inevitable deviation was encountered about the C1 thioester and C10–C11 vinyl iodide termini, a convincing level of homology was observed for all other NMR resonances in the C3–C8/C1′–C6′ region, with ^{1}H resonances within ±0.06 ppm, and all ^{13}C resonances within ±1.8 ppm of their natural product counterparts. Good correlation was also observed for $^3J_{H,H}$ couplings and key NOE enhancements between the sugar residue and the A-ring tetrahydropyran, indicative of the proposed stereochemistry.

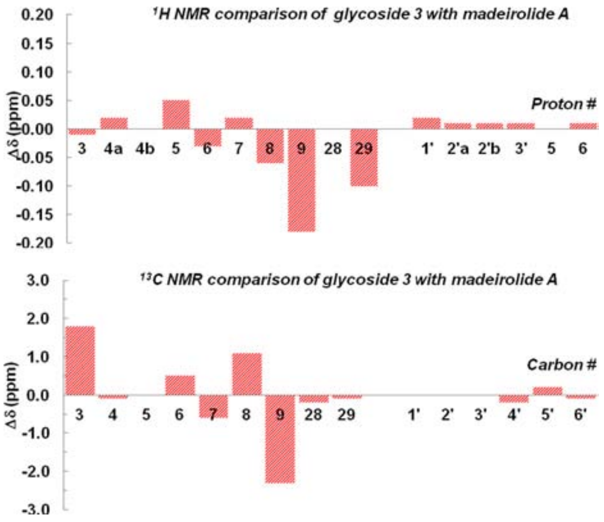


Figure 1. NMR comparison of the madeirolide A-ring glycoside **3** with madeirolide A (**1**).

In summary, we have synthesized the C1–C11 western fragment **3** of madeirolide A in 11% yield over the longest linear sequence of 17 steps from (*S*)-Roche ester derivative **11**. Importantly, the two termini of **3** are appropriately functionalized for a convergent union with the proposed eastern fragment **4** in order to complete the macrocycle. Work toward this end will be reported in due course.

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Supporting Information Available. DP4 computational NMR analysis, experimental procedures, and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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[26] The low yield obtained was primarily due to a competitive reductive deacetylation process, producing the corresponding tetrahydropyran.

[27] See the Supporting Information for details.